

Genomic Causes of Sudden Cardiac Arrest

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Received date: September 28, 2016; Accepted date: October 28, 2016; Published date: October 31, 2016

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Abstract

Sudden cardiac arrest (SCA) is a sudden and unexpected pulseless condition that typically arises from an arrhythmia. There are several bases for SCA including structural and nonstructural causes, occlusive coronary diseases, aortic diseases and other non-genomic factors. Genomics is the study of the function and interactions of the DNA in a genome. Over the past few years there has been a significant increase in what we know about the human genome and technologies based around studying the entire genome. Clinical genome and exome sequencing is currently allowing us to analyze, effectively treat, and manage patients with some of the most elusive causes of SCA. The purpose of this article is to review and outline the genomic bases, clinical presentations, family member implications, and the role of genetic counseling for some of the disorders that predispose individuals for SCA.

Keywords: Sudden cardiac arrest; Cardiomyopathy; LQTS; Genome; Exome; Genetic counseling; Brugada syndrome

Abbreviations SCA: Sudden Cardiac Arrest; HCM: Hypertrophic Cardiomyopathy; DCM: Dilated Cardiomyopathy; ARVC: Arrhythmogenic Right Ventricular Cardiomyopathy; LQTS: Long QT Syndrome; BrS: Brugada Syndrome; CPVT: Catecholaminergic Polymorphic Ventricular Tachycardia; SNP: Single-Nucleotide Polymorphism; ECG: Electrocardiogram; FH: Familial Hypercholesterolemia; CAD: Coronary Artery Disease; LDLR: LDL-receptor; PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9; LDL: Low-Density Lipoprotein; LDL-C: LDL-Cholesterol; HTN: Hypertension; LV: Left Ventricle; CGES: Clinical Genome and Exome Sequencing; MYH7: Beta Cardiac Myosin Heavy Chain; TTN: Sarcomere Protein Titin; LMNA: Lamin A/C; RYR2: Ryanodine Receptor 2; CASQ2: Calsequestrin-2; VT: Ventricular Tachycardia; VF: Ventricular Fibrillation; TMEM43: Transmembrane Protein 43; DSP: Desmoplakin; PKP2: Plakophilin-2; DSG2: Desmoglein-2; DSC2: Desmocollin-2; JUP: Junction Plakoglobin

SCA Introduction

Sudden cardiac arrest (SCA) is defined as a sudden and unexpected pulseless condition that typically arises from an arrhythmia [1]. Over 300,000 people experience SCA annually and this number accounts for approximately 20% of total mortality and 50% of cardiovascular mortality in the United States [2]. Approximately 70% of SCA is caused by structural cardiac disease with a majority of these causes containing an inherited component. It has been proposed that up to 40% of SCA cases reveal inherited cardiac disease upon genetic examination [3,4].

The etiology of SCA can be broadly distinguished based on the presence or absence of structural cardiac disease. Structural causes include, but are not limited to, ischemic and nonischemic cardiomyopathies, hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC). Nonstructural causes of SCA often stem from channelopathies such as acquired and congenital long QT

syndrome (LQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT). Classification of SCA also spans occlusive coronary artery disease, aortic diseases, and non-genomic causes. The etiology of SCA is frequently subject to the age-related distribution for the population(s) discussed. Recent studies indicate that the elderly are more susceptible to SCA due to coronary artery diseases, whereas the younger populations show a tendency towards coronary anomalies and/or genetic variations [5,6].

Genomics

Genetics encompasses the study of individual genes, heredity patterns, and interactions with the environment. The entire set of genetic instructions found in a cell is termed the genome. A new and evolving field, genomics is the study of the function and interactions of the DNA in a genome [7]. It is important to note that there is no "normal" human genome sequence. Specific locations in the human genome in which differences occur between individuals are generally referred to as variations. The terms "normal" and/or "wild type" are often used to describe the most common variant at a location in a given population. At the DNA sequence level humans are very similar; approximately 99.6% of base pairs are identical from person to person [8]. The basis of genomic variations can be divided into three categories: single-base-pair changes (point mutations), insertions and deletions, and structural rearrangements. A variant may be benign (referred to as a polymorphism) or pathogenic (referred to as a mutation) [9]. The most common variants of the human genome are single-nucleotide polymorphisms (SNPs) which are single-nucleotide variations of the genetic sequence [10,11].

Inheritance patterns are not always accurate due to incomplete penetrance and variable expressivity. For instance, an individual who displays long QT syndrome (LQTS) may exhibit incomplete penetrance. This individual has a positive genotype and may display a markedly prolonged QT interval (QTc) (the mutation is penetrant), have a normal QTc (the mutation is not penetrant), or have some abnormal alteration in the QTc (the mutation is variably expressed) [12]. Genetic determinants underlying incomplete penetrance and

variable expressivity are still poorly understood, but there are several important demographic and environmental modifiers of a particular phenotype. Gender is a known modifier of both electrocardiogram (ECG) phenotypes and risk of SCA in LQTS and BrS. Differences in hormonal effects of the cardiac ion channels are believed to be linked to this gender-phenotype relationship. Age-related changes to the heart, particularly depolarization abnormalities in BrS, also appear to influence the clinical phenotype. Lastly, exogenous influences such as electrolyte disturbances (i.e. hypokalemia), drug interactions, or even hyperthermia can unveil concealed ECG and arrhythmic manifestations of genetic mutations in LQTS and/or BrS [13].

Genomic Etiologies of SCA

Occlusive coronary artery diseases

The most common genomic etiology of the occlusive coronary artery diseases is familial hypercholesterolemia (FH). This disorder is associated with increased risk for coronary artery disease (CAD) and SCA, especially in the younger population. Mutations of the LDL-receptor (LDLR), apolipoprotein B, or proprotein convertase subtilisin/kexin type 9 (PCSK9) genes are commonly associated with causes of FH. It is important to note that >90% of FH cases are due to mutations in the genes for LDLR [14]. Individuals with FH have elevated levels of low-density lipoprotein (LDL), a plasma marker for LDL-cholesterol (LDL-C), from birth. Untreated men and women have a chance, 50% and 30% respectively, of developing CAD by the age of 55 [15]. Conversely, a 2013 paper published by Cohen [16] discusses a loss-of-function mutation in the gene for PCSK9, which results in “significantly decreased LDL-cholesterol levels and a disproportionately large reduction in coronary heart disease by reducing the exposure to LDL-cholesterol throughout life.” The mutation in this gene results in LDLR degradation and a decreased ability to bind LDL. Mutations in these particular genes decrease LDL-C uptake and clearance by the liver, provoking cholesterol deposits throughout the body [16]. Deposition of cholesterol in the coronary arteries predisposes individuals to myocardial infarction, ventricular arrhythmias, and SCA.

Structural myocardial diseases

Structural myocardial diseases are a group of heart muscle disorders which are classified by definitive cardiac structural abnormalities in the absence of secondary causes such as CAD, hypertension (HTN), valvular/overload diseases, congenital heart disease, etc. A large group of disorders, referred to as cardiomyopathies, fall into this category of diseases and will be the focus of this section.

Hypertrophic cardiomyopathy (HCM) is characterized by unexplained and typically asymmetric hypertrophy of the left ventricle (LV). HCM has a staggering prevalence of 1:500 persons in the general population and is the leading cause of SCA in young adults and young athletes [2,5,17]. Clinically, these patients may present with chest pain, palpitations, and/or syncope; however, SCA may also be the first manifestation of this disease [2]. HCM patients with sarcomere-positive mutations have a greater likelihood of LV dysfunction and a 4.3-fold increase in combined endpoints of SCA [6]. Elevated levels of sarcoplasmic calcium have been noted in mouse models with HCM which, in itself, can predispose individuals to arrhythmias and SCA [18].

In May 2013 Lombardi [2] acknowledged >900 mutations in 20 genes identified in relation to HCM. In February 2014 this figure climbed to >1400 mutations as published by Efthimiadis et al. [17]. We predict this number will continue to rise with the advancements in clinical genome and exome sequencing (CGES) and SCA studies. HCM follows an autosomal dominant inheritance. The most commonly associated genes with HCM code for cardiac myosin heavy chain- β (MYH7) and myosin-binding protein C, this is why HCM is well known as a disease of the sarcomere, the contractile apparatus of the cardiac muscle [2,19]. A recent study published in June 2014 by Bos et al. [20] indicated that up to 85% of genotype-positive patients with HCM suffered mutations in the genes for MYH7 and myosin-binding protein 3. These mutations lead to protein defects, reduced myofilament shortening, and disarray of myocytes, fibrosis, and eventual hypertrophy of the cardiac muscle. Diagnosis of HCM is usually made by echocardiogram or MRI. Current guidelines suggest diagnosis with maximum wall thickness ≥ 15 mm or mild thickening (13-14 mm) with a positive family history of HCM and/or an HCM-compatible ECG [17].

Dilated cardiomyopathy (DCM) is primarily a disease of the myocardium and has features of LV dilation, systolic dysfunction, myocyte death, and myocardial fibrosis [18]. DCM has a high prevalence of approximately 1: 2500, is the third leading cause of heart failure, and the most common reason for cardiac transplantation [2]. Ventricular dilation occurs prior to the onset of clinical symptoms. Once compensatory mechanisms of the heart fail patients present with symptoms of heart failure: decreased cardiac output, fatigue, dyspnea on exertion, chest pain, arrhythmias, syncope and/or SCA [2].

Approximately 35% of these cases are considered ‘idiopathic’ and may be caused by genetic mutations [5]. DCM is attributable to mutations in over 50 genes [2] and is typically inherited via autosomal dominant patterns, but autosomal recessive (1-2% of cases) and X-linked (5-10% of cases) variations have been identified [6,18]. The gene encoding the sarcomere protein titin (TTN) has been identified as the most common known genetic cause of DCM, with mutations in this gene occurring in 25% of familial cases and 18% of sporadic cases [21]. Titin is a major component of the cardiac sarcomere [22] and is anchored to the Z disc, which plays a pivotal role in several aspects of cardiac force generation and transmission [23]. Other commonly implicated genes include lamin A/C (LMNA), alpha myosin heavy chain, beta myosin heavy chain (MYH7), troponin T, myosin-binding protein C, the cardiac sodium channel, genes of the desmosomes, and an alternative splicing regulator of many transcripts [5]. Genetic testing for DCM, other than the TTN gene, has a relatively low yield of $\leq 20\%$ [2].

Arrhythmogenic right ventricular cardiomyopathy is a disease of myocyte loss, fibrofatty infiltration of the myocardium, and increased susceptibility to arrhythmias and SCA. ARVC, as its name implies, is predominantly a disease of the right ventricle but has also been associated with left ventricular infiltration. This particular disorder is linked to a significant proportion of SCA in young adults and athletes. The prevalence of ARVC has increased over the years and is now thought to occur in 1 in 2000-5000 individuals. Up to 50% of cases are believed to be hereditary as ARVC exhibits autosomal dominant inheritance in most cases, autosomal recessive cases have been suggested [2], and 80% of individuals are diagnosed before the age of 40 [24]. ARVC is predominantly a disease of the desmosome, an intercellular component that forms cell-to-cell junctions. Mutations in the genes encoding these desmosomes compromise cellular adhesions

and decrease the ability of the myocyte to withstand the mechanical stress undergone during the cardiac cycle [18]. Clinically, we note symptoms of a defective transmission of contractile force. The most common presenting symptoms in patients are palpitations, syncope, and SCA ranging from 23-27% of patients [25]. However, several individuals may be asymptomatic and suffer SCA as their initial symptom. Symptomatic ventricular arrhythmias such as premature ventricular beats, ventricular tachycardia (VT), left bundle branch blocks, and/or ventricular fibrillation (VF) can all lead to the SCA associated with ARVC [25].

There are eight commonly associated genes that code for proteins that can lead to ARVC if mutated: transforming growth factor beta-3, ryanodine receptor 2 (RYR2), transmembrane protein 43 (TMEM43), desmoplakin (DSP), plakophilin-2 (PKP2), desmoglein-2 (DSG2), desmocollin-2 (DSC2), and junction plakoglobin (JUP). Of these eight genes there are five (PKP2, DSG2, DSP, DSC2, and JUP) which encode major components of the cardiac desmosome. It should be noted that PKP2 is the most commonly associated genotype with ARVC in up to 43% of cases [6].

Non-structural arrhythmogenic disease

Non-structural arrhythmogenic diseases are often referred to as cardiac channelopathies. These diseases are defined as primary electrical disorders in structurally normal hearts which are typically caused by mutations in genes which encode ion channels, ion channel subunits, or regulatory proteins. Ion channels are integral membrane proteins which are responsible for the conduction across the cell membrane. Ion channel subunits contain a large number of subunits which are encoded for by several genes [2,26]. Several channelopathies have been associated with altering sodium (Na⁺), potassium (K⁺), and/or calcium (Ca²⁺) ion currents which can ultimately influence the generation of action potentials and calcium homeostasis.

LQTS is a potentially life-threatening cardiac arrhythmia characterized by delayed myocardial repolarization which produces QT prolongation, predisposing patients to ventricular arrhythmias and increasing risk of SCA [2,27]. LQTS accounts for 20% of autopsy-negative unexplained sudden deaths in the younger population. Clinical presentation of LQTS may include palpitations, presyncope, syncope, or SCA. SCA is the first event in 5% of asymptomatic individuals [2].

LQTS exhibits autosomal dominant inheritance and there are more than 600 mutations that have been identified in 13 LQTS genes [6,28]. The three major genes linked to LQTS are KCNQ1, KCNH2, and SCN5A, which are responsible for LQTS type 1 (LQT1), LQT2, and LQT3, respectively. 90% of genetically confirmed LQTS are caused by mutations in these three genes [2]. KCNQ1 and KCNH2 both code for potassium channels while SCN5A codes for a sodium channel, and the vast majority of mutations in these genes are a result of SNPs or small insertions/deletions [27]. Prolongation of the QTc is a strong risk factor for future ventricular arrhythmias. The longer the prolongation of QTc, the more likely the condition will demonstrate a poorer prognosis for the individual [5]. LQT8, a less common form of LQTS, is referred to as "Timothy syndrome," is a gain of function mutation of the L-type Ca²⁺ channel, and is associated with extremely prolonged QTc [28].

CPVT is a polymorphic VT which is induced by adrenergic stimulation (e.g., vigorous exercise or fear) in the absence of structural heart disease. CPVT may present clinically in several forms such as

exercise-induced syncope or SCA or near-drowning [5]. The ECG is typically normal, but exercise testing will induce ventricular arrhythmias in 75-100% of patients [2].

There are two common forms of CPVT (type 1 and type 2) caused by mutations in the genes encoding the ryanodine receptor and calsequestrin. CPVT1 is an autosomal dominant form in which the gene for ryanodine receptor-2 (RYR2) is affected. CPVT2 is the autosomal recessive form in which the gene for calsequestrin-2 (CASQ2) is affected [2]. There are 67 individual mutations affecting the gene for ryanodine receptors and 7 mutations affecting the gene for calsequestrin which can cause CPVT; notably, mutations in the genes for RYR2 and CASQ2 are the most common of these [6]. The ryanodine receptor and calsequestrin are involved in intracellular and sarcoplasmic reticulum calcium homeostasis and, thus, excitation-contraction coupling [19]. These mutations lead to increased calcium leakage from the sarcoplasmic reticulum, increased intracellular calcium, and predisposition to cardiac arrhythmias and SCA [5,26].

BrS is an electrical conduction disorder which displays very characteristic ECG findings and predisposes individuals to SCA secondary to polymorphic VT and/or VF. According to Berne and Brugada [29] "the diagnosis of BS (Brugada syndrome) requires the presence of a type 1 BS pattern in the right precordial leads (ie, V1-V3) ...characterized by a prominent coved ST-segment elevation displaying J-point amplitude or ST-segment elevation ≥ 2 mm, followed by a negative T wave." Once a type 1 ECG pattern in the right precordial leads is observed, and other possible causes are excluded, a definitive diagnosis can be established incorporating the patient's family history, arrhythmia-related symptoms, and/or documented ventricular arrhythmias [29]. BrS accounts for 4% of overall SCA and approximately 20% of SCA in those with structurally normal hearts [2].

The majority of patients with BrS exhibit sporadic mutations. BrS exhibits an autosomal dominance inheritance pattern and has approximately 300 mutations in 14 different genes that are responsible for the clinical disease [19]. The most common mutation related to BrS is found in the SCN5A gene, leads to a loss of function in the cardiac Na⁺ channel, and is present in approximately 20% of BrS cases. It should be noted that the type 1 pattern can be concealed, variable, or induced by sodium-channel blocking medications (e.g., Ajmaline or Flecainide) [29].

Aortic diseases

With the discussion of aortic diseases it is common to discuss the genomic causes in two categories: syndromic and non-syndromic causes. Syndromic causes typically display a characteristic pattern which classifies a particular condition, whereas non-syndromic causes are disease manifestations which occur in isolation from other characteristic signs or symptoms. Syndromic causes of aortic disease are often seen with conditions such as Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS), and Ehlers-Danlos syndrome (EDS). Non-syndromic causes of aortic disease are typically seen in single-gene mutations such as in those affecting myosin heavy chain 11 and transforming growth factor receptors 1 and 2 [30].

MFS is one of the most commonly identified diseases predisposing individuals to aortic aneurysms. MFS is typically caused by a mutation in the gene encoding fibrillin 1 and occurs worldwide, affecting approximately 1 in every 5000 individuals [30]. MFS exhibits an autosomal dominant inheritance pattern. Fibrillin 1 is an important

structural component that plays a key role in the mechanical strength of the aortic wall. Fibrillin 1 also plays a key role in homeostasis of growth factors and other microfibrillar proteins in the extracellular matrix, such as transforming growth factor beta (TGF β) and bone morphogenic proteins [31]. Mutations in the gene encoding fibrillin 1 therefore lead to an altered protein that causes an increase in the TGF β signaling pathway and classically display symptoms such as skeletal overgrowth, ocular lens dislocation, aortic aneurysms/dissections, and/or mitral/aortic valve insufficiency [32].

LDS is another syndromic aortic disease which is caused by a mutation in the genes encoding transforming growth factor receptor 1 and 2. LDS displays typical dysmorphic features, separated into 2 categories: LDS type 1 and LDS type 2. In LDS type 1 individuals will present with or have a history of hypertelorism, craniosynostoses, and/or cleft palate; while individuals with LDS type 2 may display hypertelorism, translucent skin, easy bruising and atrophic scarring [30]. LDS displays an autosomal dominant inheritance pattern. Interestingly enough, LDS displays the same mechanisms of increased TGF β activity as in MFS. Again, this highlights the theories behind dysregulated TGF β signaling pathways and aneurysm formation [31]. Mutations in the genes for either TGF β R1 or TGF β R2 predispose patients to aggressive vascular disease [33].

The vascular type of Ehlers Danlos syndrome, type IV, is almost exclusively a result of a mutation in the gene for type III procollagen (COL3A1). EDS type IV is inherited in an autosomal dominant fashion where 50% of mutations in the COL3A1 gene arise from an affected parent and the remaining 50% are de novo [34]. Clinical symptoms of EDS type IV are characterized by translucent skin susceptible to easy bruising, arterial, intestinal, and uterine rupture [30,34]. The majority of adults with EDS type IV will demonstrate vascular aneurysms/dissections or gastrointestinal perforations as presenting features with the average age of these patients being 23 [30].

The non-syndromic causes of aortic disease have been shown to predispose individuals to thoracic abdominal aortic dissections and interfere with vascular and non-vascular smooth muscle contractility [35]. Genes encoding proteins such as TGF β 1 and TGF β 2 play roles in syndromic processes but are also responsible for non-syndromic aortic diseases for similar reasons. Mutations in the gene encoding myosin heavy chain 11 account for 2% of non-syndromic thoracic abdominal aortic dissections and have been known to be associated with patent ductus arteriosus (PDA) [36]. Mutations in the gene encoding protein actin alpha 2 are the most common mutations that result in aortic aneurysms, accounting for up to 15% of all familial thoracic abdominal aortic aneurysm mutations. The actin protein plays a large role in vascular smooth muscle contraction because it interacts with β -myosin heavy chain [30].

Regardless of the cause for the aortic aneurysm/dissection all of these disorders place the individual at risk for SCA. When an aortic dissection occurs and blood escapes into the extravascular spaces (e.g., the mediastinum or peritoneum) the body will attempt to compensate by increasing vascular tone and heart rate. If blood loss is significant there will be insufficient amounts of intravascular fluid to distribute to organs, such as the heart, which will evoke life-threatening arrhythmias and eventual cardiac arrest.

Non genomic etiologies

Non-genomic causes of SCA encompass a multitude of modifiable risk factors commonly associated with CAD. Genes we inherit cannot

be controlled but certain factors we can control that place us at increased risk for SCA are: tobacco exposure, high blood pressure, high cholesterol (lifestyle-based), obesity, diabetes, and/or physical inactivity. A 2012 meta-analysis conducted by Berry et al. [37] concluded that having more risk factors, such as those previously indicated, are positively associated with lifetime risk of death from cardiovascular disease.

New genomic technologies

CGES has entered the medical practice with goals of establishing diagnoses for nonspecific or unusual disorders that are suspected to be genetic in origin [38]. We believe CGES will be the most influential predictive tool for implementing individualized medicine in the future of healthcare. Population screening will increase in frequency to determine individual susceptibilities for common disorders such as heart disease, diabetes, and cancer [39].

Clinical genome and exome sequencing

CGES is a single comprehensive test that examines essentially all human genes. Whole genome sequencing analyzes all areas covered by the genome and this differs from whole exome sequencing, which is focused on approximately 2% of the genome that is known to code for proteins. The entire purpose of CGES is to determine the base sequences of human DNA, align these sequences with reference sequences, and identify specific base pair variations [40]. This type of sequencing is most useful for the detection of SNPs or deletions of 8-10 nucleotides or smaller. Whole exome sequencing is quite unique in that it typically covers 95% of the exons, which contain 85% of disease-causing mutations in Mendelian disorders and many SNPs which predispose individuals to particular disorders [41]. This sequencing technology will discard many limitations that were set forth by older models and genetic analysis techniques and shorten diagnostic times for several clinically complex cases [24].

CGES implications for patient and family

It is of utmost importance that clinicians understand the indications for CGES so it may be effectively implemented in their daily practices. Success rates for CGES in determining causative variants has been documented around 25%, which is higher than the positive rates of other genetic tests such as karyotype analysis (5 to 15%), chromosomal microarray analysis (15 to 20%), and Sanger sequencing for single genes [42]. This reputable statistic should not distract clinicians from realizing that CGES should be performed on those individuals who will most benefit from its results. CGES is currently indicated for the detection of rare variants suspected to be due to Mendelian (single-gene) genetic disorders after previously recognized single-gene possibilities have been eliminated [38].

The HRS/EHRA Consensus Statement by Ackerman et al. [43] offers an in depth perspective into this particular portion of this review, and thus will be used as a primary resource. We will be discussing recommendations regarding CGES and the underlying etiologies of SCA.

The National Institute of Health and Clinical Excellence in the UK published work in 2008 recommending genetic testing of index cases with FH and subsequent testing of family members due to the increasing prevalence of this disease [14]. With the latest recommendations of proper dietary habits, the advent of cholesterol-reducing medications, and the availability of CGES early intervention

will be pivotal in reducing SCA and other comorbidities that are a result of FH. In children who are genetically diagnosed with FH there are recommendations that support the intervention of statin medications as early as the age of 8 in certain cases (e.g., LDL-C persistently ≥ 190 mg/dL after 6 months of a stringent diet, coupled with the positive family history) with the goal of therapy to reduce LDL-C to values ≤ 130 mg/dL [44]. Family members diagnosed with FH should seek healthy lifestyle modification to include dietary fat restriction and routine exercise in conjunction with medication therapy. These guidelines also apply to non-genomic, modifiable causes of SCA.

Genetic testing is recommended in any patient with a strong clinical diagnosis of HCM where mutation-specific sequencing would benefit family members. Currently, there is no evidence to support that early detection of HCM will change the course of the disease, but early intervention will improve lifelong management of the patient or family members [17]. Greatest benefit would be attributed to (a) families with a history of SCA, (b) families with multiple potential relatives at risk, and (c) families where clinical diagnosis is otherwise difficult (e.g., several members of a family suffer from clinically correlated HCM findings but display mild hypertrophy). Variant-specific sequencing is also recommended post-mortem on individuals who suffered SCA where HCM had not been previously identified in the family [43]. The Mayo HCM Genotype Predictor [20] was recently developed to predict the likelihood of a positive genetic test result. This predictor score is based on 6 factors: age at diagnosis, maximum LV wall thickness, family history of HCM and/or SCA, shape of the septum, and history of hypertension. The likelihood of a positive genetic test result ranges from 6% to 80% based on the total score of the aforementioned clinical predictors. The more clinical markers present, the greater the probability of positive genetic mutation. It should be noted that hypertension negatively correlates with genetic HCM and is thusly attributed a negative score (-1) on the Mayo HCM Predictor Score [20]. The implementation of these guidelines and predictor score can assist clinicians in determining whether or not to pursue genetic testing.

Clinical screening of family members of patients with DCM is recommended. It was noted that 20-35% of patients with DCM had first degree relatives who were also affected, and up to almost 50% if you allow left ventricular enlargement to serve as a precursor for DCM [21,43]. The relatively low frequency of involvement of genes other than TTN in the identification of DCM makes genetic analysis particularly feeble. Patients burdened with both conduction disorders and channelopathies may have increased frequency of genetic variations in LMNA and SCN5A. LMNA variations have been associated with higher rates of SCA and should be monitored by a clinician due to the aggressive nature of this particular form of cardiomyopathy [5]. CGES should be performed on index patients with DCM and variant-specific (TTN, LMNA, and SCN5A) sequencing is recommended for primary family members or clinically affected family members.

Genetic testing for ARVC is often based on initial diagnostic criteria of ARVC set forth by the International Task Force, revised 2010 [45]. CGES or variant-specific (DSC2, DSG2, DSP, JUP, PKP2, and TMEM43) screening can be useful for individuals who satisfy the aforementioned criteria, and may be considered in those who satisfy 1 major or 2 minor criteria. Variant-specific testing is recommended for primary family members and appropriate relatives for identification of the ARVC-causative mutation in the index case. As previously

mentioned, those with ARVC genotypes may show no clinical symptoms in early stages of the disease. It is recommended that periodic physical assessments be performed in primary, secondary, and sometimes tertiary relatives to decrease the incidence of clinically undiagnosed cases of ARVC [43].

Clinical LQTS genetic testing is recommended for any patient in which LQTS is suspected, based on the findings of the clinician. These findings include, but should not be limited to, the patient's clinical history, family history, QTc, T-wave morphology, and/or responses to exercise/pharmacologically based stress testing. Genetic testing is recommended even in the absence of symptoms, the clinical phenotype, for patients with otherwise idiopathic QTc prolongation (QTc ≥ 480 ms in prepubertal children and ≥ 500 ms in adults) [43]. If a causative mutation is identified this is when variant-specific sequence testing should be performed for primary family members of the index patient. Approximately 85% of reported cases of LQTS are inherited while the other 15% are de novo mutations. The most common pattern of inheritance of LQTS is autosomal dominant but there are reported cases of autosomal recessive inheritance as well [6].

Clinical CPVT genetic testing is recommended for any patient in whom the clinician has determined a clinical index of suspicion for CPVT based on the clinical history, family history, and expressed ECG phenotype during exercise/pharmacologically based stress testing. Variant-specific sequence testing is recommended for primary family members of the index patient following the identification of the CPVT causative mutation. It is also recommended that both primary and secondary family members undergo clinical and genetic evaluation, including a stress test, when a positive CPVT variant has been identified [43]. This is particularly important because approximately 30% of affected individuals become symptomatic by 10 years of age. Early genetic evaluation for family members is important because CPVT may present initially as SCA in the index patient, thus the evaluation may promote early treatment intervention for those affected [5].

Genetic testing for the BrS type 1 mutation (SCN5A variant) or a combination of variants can be useful for those patients with a high clinical index of suspicion as determined by the clinician. Genetic testing is not indicated when the isolated findings of BrS2 or BrS3 are found on ECG. Variant-specific sequence testing is recommended for family members following the identification of a BrS causative mutation in the index patient [43]. Recent findings by Wilde & Behr [19] indicate that families carrying a SCN5A mutation contain individuals expressing the BrS phenotype but lacking the BrS genotype; therefore, with our understanding that SCN5A mutation carriers typically display conduction abnormalities, it is suggested that these genes may actually have a role in disease modification rather than causation [19]. Sequence testing in families with underlying SCN5A mutations may play a significant role in risk stratification for the individuals of the family [43].

Diagnosis of an index patient within a family is critical in order to pursue genetic testing of the different aortic diseases. Common complex diseases leading to aortic aneurysms are likely to be multifactorial with regard to genetic risk factors. The aortic diseases discussed in this paper are typically inherited in an autosomal dominant fashion. Clinical symptomatology and/or other criteria determined by healthcare professionals should be taken into account in order to identify an index patient. Once identified, we recommend CGES of all primary family members and other family members that may be at risk of possessing mutations leading to any aortic disease

pathology. Future research is needed to focus upon CGES with a large sample size to identify genetic factors which further contribute to the development, growth and rupture of aortic aneurysms. Identifying risk factors will provide the basis for genetic testing and assist in identification of individuals with aortic aneurysms before rupture [46]. When a mutation is present in young family members it is important to monitor these individuals closely to anticipate effects of clinical diagnosis and treatment to prevent these potentially life altering complications [47]. In certain instances (e.g., mutation of COL3A1) it is considered acceptable to image the entire aorta on a periodic basis due to the possibility of thoracic abdominal aortic dissections [35].

The correct identification of the definitive disease causing genetic variants in the index patient sheds light on a gold standard diagnostic marker that may be used to evaluate family members at risk [43]. However, it is important to note that these are guidelines based on an evolving area of study and the clinician should use their best judgment as knowledge, experience, and further research is performed regarding CGES and SCA.

Genetic Counseling

Genetic counseling is a key piece of the CGES process. Pretest counseling should be performed prior to any blood draw. This is done in an effort to ensure that the individuals are prepared for what the results may show. All questions about the implications of a positive result or negative result should be framed appropriately in the individual's mind. Breaching these discussion topics ahead of time will alleviate potential sources of shame or guilt. Such feelings may arise after a positive variation is detected in an autosomal dominant trait in an individual with several children. Genetic counseling is in place to reinforce hope for the best possible outcomes and portray sound understanding of these complex topics. The terms "genetics" and "fate" are not synonymous, and thus the results of the CGES testing are not foolproof. When discussing a negative sequence result to someone who has had SCA, it is important to avoid giving complete reassurance that this will not happen to a relative. There is a complex interplay of genes and substances which is not fully understood yet, and these are areas for future research. There are cases in which a phenotype is expressed but the CGES shows no variant. For instance, if a variant-specific sequence test is negative but a patient exhibits prolonged QTc then sequence reevaluation should be performed and independent comprehensive LQTS genetic testing should be considered [43].

The genetic counselor also has an important responsibility in collaborating with physicians, medical geneticists, and phenotypically-affected individuals who should be considered for CGES. The genetic counselor and physician should utilize evidence-based criteria for these particular individuals, for instance: (a) a patient presents with a defined genetic disorder displaying profound genetic heterogeneity (b) a patient presents with a likely genetic disorder but single-variant analysis for known disorders has yielded no result or (c) a patient presents with a phenotype and/or strong family history that indicates a particular genetic etiology, yet the phenotype does not correlate to a specific gene for targeted sequencing [48]. The counseling process can be eased by addressing an individual's particular motivation(s) either for or against the pursuit of genetic testing [49]. Communication between the genetic counselors, the patient, and any at-risk family members is extremely important and thus should always remain a priority.

When evaluating a CGES result it is important to keep in mind the considerations of analytic validity and clinical validity. Analytic validity pertains to the accuracy of the results. CGES has a highly accurate true-positive result, but the false-negative rates may vary depending upon the region of the genome of interest [38]. Regardless of the disease in question, treatment decisions should not solely depend on the outcome of the CGES but should be based upon the results of a comprehensive and holistic clinical evaluation [43].

Conclusion

There are several bases for SCA including structural and nonstructural causes, occlusive coronary diseases, aortic diseases and other non-genomic factors. The first clinical presentation of SCA is often lethal, necessitating early patient identification and primary prevention strategies. Genetic profiling through CGES allows us to analyze, effectively treat, and manage patients with several causes of SCA. In addition to CGES, other strategic approaches, such as ECG screening and radiographic imaging, provide beneficial information with regard to primary prevention in the population. The field of inherited arrhythmias and other cardiac tissue pathology has seen a great deal of change over the past 10-20 years predominantly due to genetic diagnosis. With this in mind, there are still vast populations of patients who die prior to diagnosis. There are several knowledge gaps that remain in risk-stratification and early identification of these conditions and further research is necessary to impact these factors. Specific guidelines have been proposed for the differing inherited clinical syndromes, which are detailed in this manuscript. General population universal guidelines may be applied to all victims of SCA, wherein their blood should be analyzed for molecular pathology and screening of family members should be implicated based on these results.

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